Chemistry 17: Section Handout 7

Topics: *chirality, stereocenters, stereoisomers, absolute and relative stereochemistry, conformational analysis, bond rotations, ring strain, cyclohexane conformations*

Key Concept Review

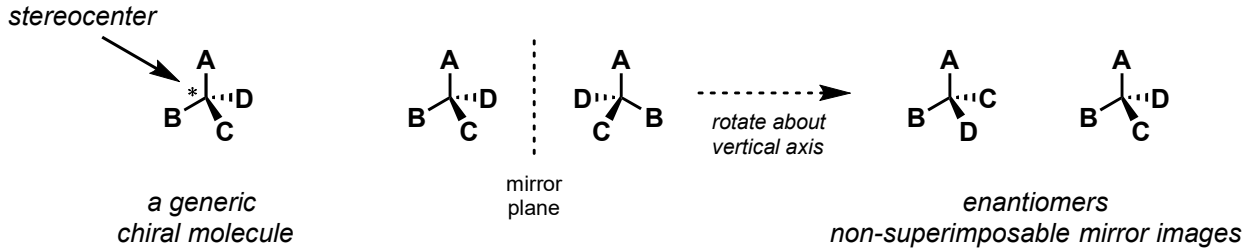
Stereochemistry: Refers to the spatial arrangement of atoms or groups within a molecule.

Chiral: Describes a molecule that is not superimposable on its mirror image. A chiral molecule exhibits optical activity by rotating plane-polarized light, and does not have a plane of symmetry.

Achiral: Describes a molecule that is superimposable on its mirror image. An achiral molecule does not exhibit optical activity, and will commonly possess a plane of symmetry.

Stereocenter: An atom (usually tetrahedral carbon) with four distinct atoms or groups attached to it.

Enantiomers: A pair of chiral molecules that are non-superimposable mirror images. Enantiomers have the same connectivity and differ only in the spatial arrangement at each stereocenter. If multiple stereocenters are present in a single molecule, a pair of enantiomers must be mirror images at every stereocenter (have the opposite R/S configuration). Enantiomers have identical physical properties and have the same energy on a reaction coordinate diagram. They differ only in their interactions with a chiral environment (ie. other chiral molecules, plane-polarized light).



Examples of enantiomers:

L-Alanine *D*-Alanine (*R*)-1-phenylethanol (*S*)-1-phenylethanol

Racemate (i.e. racemic mixture): A 50:50 mixture of two enantiomers of a compound. Although each enantiomer in the mixture is optically active, the racemic mixture will not exhibit optical activity because there is no net rotation of plane-polarized light.

Diastereomers: Molecules that are configurational isomers but not enantiomers. Diasteromers can arise from differences in configuration at stereocenters or at alkenes, and they may be achiral. Diastereomers differ in their physical properties and chemical reactivity. Diastereomeric molecules with multiple stereocenters will have at least one stereocenter of the same configuration and at least one that is different.

Examples:

trans-2-methylstyrene *cis*-2-methylstyrene *cis*-1,2-diaminocyclohexane *trans*-1,2-diaminocyclohexane

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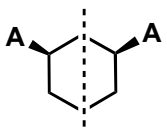
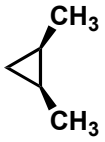
Meso compounds: A molecule containing two or more stereocenters that also possesses a plane of symmetry, which renders it superimposable on its mirror image. Meso compounds are achiral and cannot have enantiomers. A meso compound will always have a chiral diastereomer. Meso compounds are optically inactive.

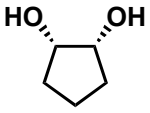
plane of symmetry

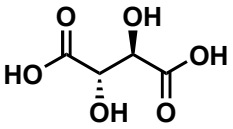


a generic meso compound

Examples:







2^n rule: A molecule with n stereocenters will have a maximum of 2^n stereoisomers. This number will be reduced in the presence of internal symmetry, such as with meso compounds. We include alkenes that lead to E/Z isomers as stereocenters.

Stereospecificity: Refers to a mechanism in which the stereochemistry of the products is dictated by the stereochemistry of the starting material. A "non-stereospecific" mechanism is one in which stereochemical information is lost. A stereospecific mechanism in which the products have the same configuration as the starting material proceeds with *stereoretention*. A stereospecific mechanism in which the products have the opposite configuration as the starting material proceeds with *stereoinversion*.

Stereoselectivity: Refers to a non-stereospecific mechanism in which the stereochemical outcome is controlled externally (ie. by a chiral catalyst).

Prochirality: The potential for an achiral molecule to be converted to a chiral molecule in a single chemical step.

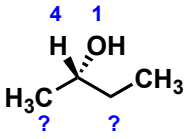
Absolute configuration: The spatial arrangement of atoms or groups around a stereocenter that, as determined by the Cahn-Ingold-Prelog rules, leads to the description as *R* or *S*.

The Cahn-Ingold-Prelog (CIP) Convention: The CIP convention provides a set of rules that are used to assign the absolute configuration at a stereocenter. To assign a configuration to a stereocenter:

1. Assign a "priority" to each atom (1-4) attached to the stereocenter, with the highest atomic number having the highest priority.

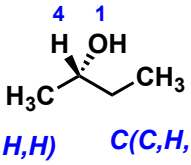
Example

Step 1



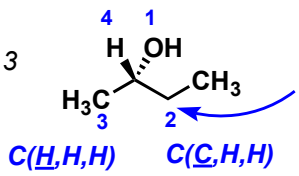
2. If the stereocenter has identical atoms attached to it, write out the substituents on these atoms, in the order of their priority (again with higher atomic number having a higher priority). A multiple bond is counted as multiple atoms (for example a double bond to oxygen counts as two oxygen atoms).

Step 2



3. Keep listing out the substituents of the two identical atoms in order of priority until you reach a difference. At this point, give the higher priority to the atom with the higher priority substituent.

Step 3



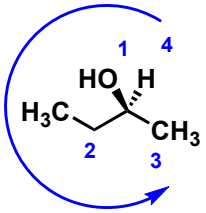
This atom has a C and 2 H's, so this group is a higher priority substitutent than the carbon with 3 H's, because C has a higher atomic number than H.

4. Orient the molecule so that the lowest priority group is pointing backwards. Consider the arrangement of the other three substituents, from highest priority to lowest priority.

- If the substituents are arranged in a ***clockwise*** fashion, the stereocenter is ***"R"*** *(sho*rt for rectus).

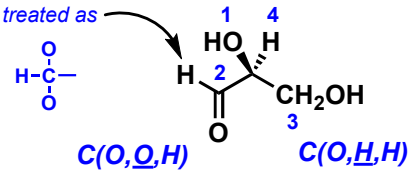
- If the substituents are arranged in a ***counter-clockwise*** fashion, the stereocenter is ***"S"*** *(sho*rt for sinister).

Step 4

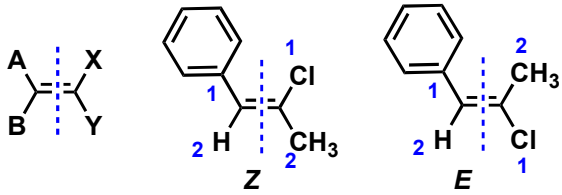


*In this case, the substituents are ordered in a counter-clockwise arrangement, and the stereogenic center is assigned as **S***

5. If substituents contain multiply-bonded atoms, treat each bond to the atom in the multiple bond as if it were to a separate atom then list these substituents in order of priority.



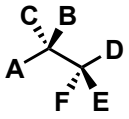
Assigning *E/Z* to alkenes: Using the CIP rules, compare the priority of the two groups at each end of the alkene (A vs B, and X vs Y). If the two higher priority groups lie on opposite sides of the double bond, the configuration is *E* (short for *entgegen* or opposite), if on the same side the configuration is *Z* (short for *zusammen* or together).



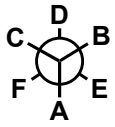
Conformational Analysis: Conformational isomers (or "conformers") are stereoisomers that may be interconverted by rotation about one or more single bonds. Conformational isomers are considered identical molecules, although they differ in their arrangement in three-dimensional space, because they can generally interconvert rapidly. Conformational analysis involves the study of the accessible conformations of a molecule and the use of that information to predict and explain that molecule's reactivity.

Representing conformations: Depending on the information you hope to obtain or convey about the shape of a conformer, it may be helpful to draw it in a different form. You should become comfortable with representing structures in each of these forms and interconverting between styles; a model kit will be invaluable in this process.

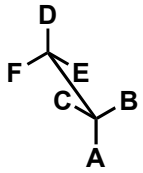
• *Line/Skeletal Drawings: "*zig-zag" representations of molecules in which carbon atoms are implied at each point and terminus of the zig-zag. Wedges are used to indicate that a group projects out of the page. Tapered hashes are used to indicate that a group projects into the page. Straight lines indicate that the group lies in the plane of the page.



• *Newman Projections: "*end-on" representations of molecules in which the compound is drawn looking down the axis of a bond such that the front atom in the bond obscures the back atom. The atom nearer to the viewer is represented by the three bonds to its substituents coming together in a Y shape. The atom further from the viewer is represented by a large circle, and the substituents on this atom are drawn from the edge of this circle. Newman projections are exceptionally useful for portraying staggered, gauche, and eclipsed conformations.



• *Sawhorse Projections:* perspective drawings of molecules, midway between skeletal drawings and Newman projections, in which the central bond is elongated and drawn at an angle to allow all substituents about that bond to be represented clearly. Sawhorse projections are especially useful for representing the reactive conformations of acyclic molecules.

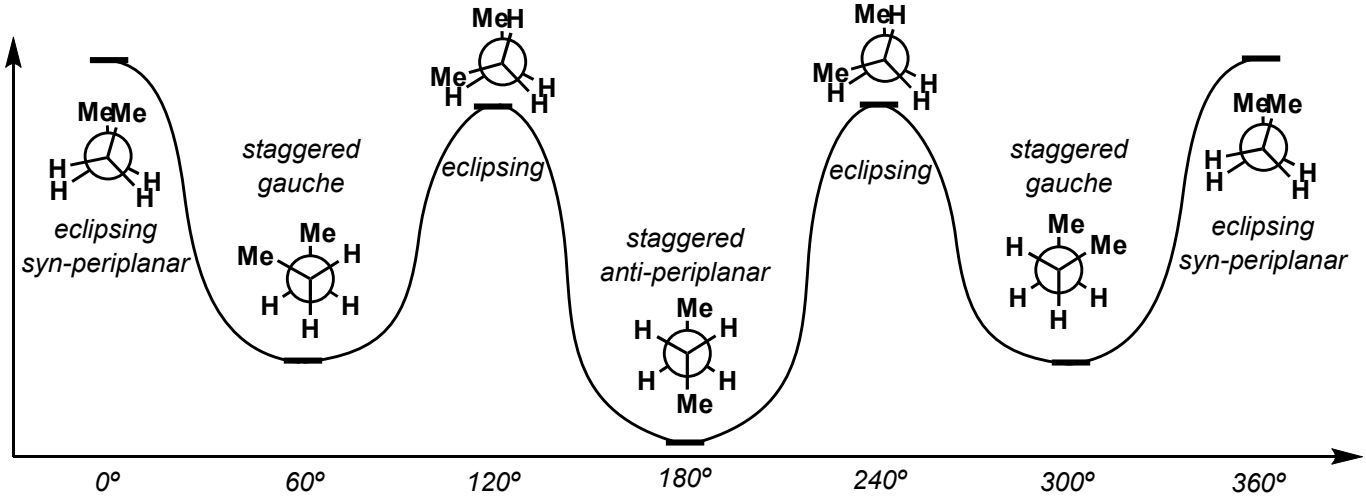


Conformational analysis for acyclic systems: Rotation about single bonds is rapid, and it proceeds through local energetic minima (in which substituents are staggered) and local maxima (in which substituents are eclipsed).

• *Eclipsing Interaction: The*re is an energetic penalty (for steric and stereoelectronic reasons) for orienting groups with a 0º dihedral angle; this is called an "eclipsing" orientation. The penalty is ~1.0 kcal/mol for each H–H eclipsing interaction, ~1.4 kcal/mol for each C–H eclipsing interaction, and ~3 kcal/mol for each C–C eclipsing interaction.

• *Gauche Interaction: The*re is a smaller energetic penalty (for steric reasons) for orienting large groups at a 60º dihedral angle relative to each other; this is called a "gauche" orientation. The penalty is ~0.9 kcal/mol for each C–C gauche interaction.

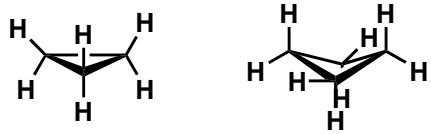
Consider the conformations of butane as the central bond rotates through 360º.



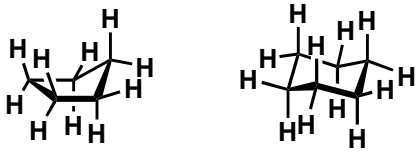
Dihedral Angle

• R*ing Strain: The* bond angles in cyclic all-sp^3 molecules will not necessarily be able to reach the ideal 109º corresponding to a perfectly tetrahedral carbon. Deviations from the ideal angle will lead to poor physical overlap between the bonding orbitals, resulting in weaker bonds; this is described as bond-angle strain. Ring strain includes terms for bond-angle strain and for the energetic pentalty for repulsive steric interactions between eclipsing and gauche substituents on the ring.

Small Rings

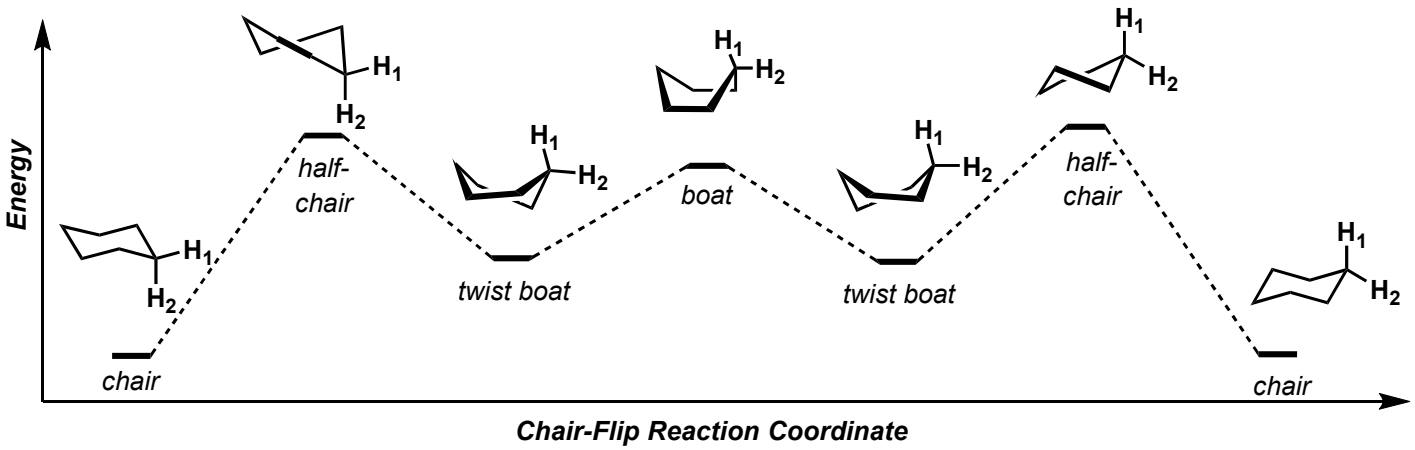


Normal Rings



- *Small rings* (3- and 4-membered rings) experience significant ring strain due to both bond-angle strain and repulsive stereic interactions between eclipsing substituents. As such, they tend to be particularly reactive through mechanisms that release that ring strain.
- *Normal rings* (5-, 6-, and 7-membered rings) can adopt non-planar conformations that allow them to minimize bond-angle strain and eclipsing interactions. Cyclohexanes (6-carbon rings) are strain-free, and exceptionally important in conformational analysis.
- *Medium rings* (8- to 14- membered rings) also adopt non-planar conformations; while they are generally able to avoid significant bond-angle strain, repulsive steric interactions remain problematic and destabilize these rings

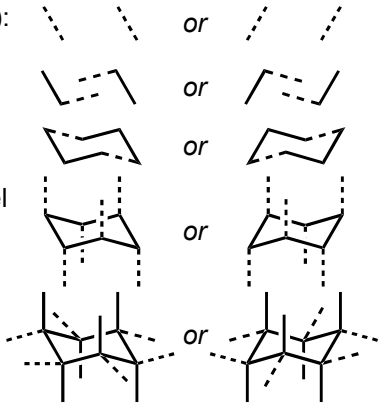
• C*onformations of Cyclohexane: Cy*clohexane is strain-free due to its ability to access a chair conformation with no bond-angle strain and a completely staggered arrangemet of ring substituents. Cyclohexane can, however, access a range of other conformers in the process of undergoing a "chair-flip" or ring inversion, in which all of the equatorial H's are moved to an axial position and all of the axial H's are moved to an equatorial position.



Chair-Flip Reaction Coordinate

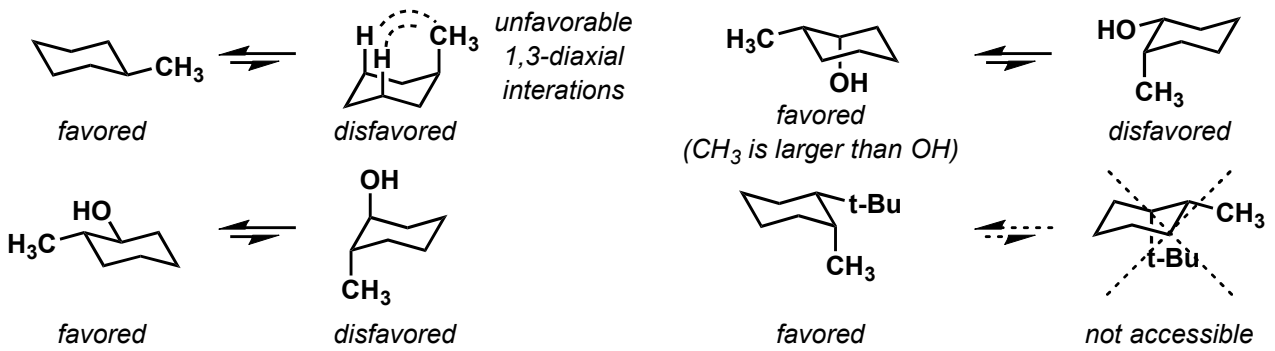
• *Steps for Drawing a Chair Cyclohexane (*See Clayden, page 371 for an alternate strategy and choose the method that gives you the tidiest and most consistent results):

1) Draw in two parallel lines of equal length tilted slightly to the left or right; these lines will be the "ends" of your cyclohexane.
2) From the "inside" corners, draw two more parallel lines of equal length, tilted slightly up or down.
3) From the "outside" corners, connect the remaining corners with two more parallel lines of equal length.
4) Draw in all of the axial substituents. Note that three point straight up and three point straight down.
5) Draw in all of the equatorial substituents in a zig-zag such that these lines are parallel to the lines you drew in steps 1-3. Note that three of point slightly up and three point slightly down.



Note: "Axial" and "equatorial" are NOT synonymous with "up" and "down". All of the "up" substituents alternate between axial and equatorial positions proceeding around the ring; all of the "down" substituents alternate between equatorial and axial positions proceeding around the ring in the same fashion.

• C*hair Conformations of Substituted Cyclohexanes: Th*ere is an energetic difference between putting (non-hydrogen) substituents in an axial position vs. an equatorial position due to the repulsive 1,3-diaxial interactions present in the axial position. As such, as the size of a substituent increases, it's preference for remaining in the equatorial position will increase. The energetic preferences for placing a range of substituents in the equatorial position have been tablulated as "A-values". When two substituents have competing preferences, the substituent with the larger "A-value" will control the favored conformation of the the substituted cyclohexane. Te*rt-b*utyl groups suffer such a large steric penalty in the axial position, that they lock the substitued cyclohexane rings into the single conformation that places the t-*b*utyl group equatorial.

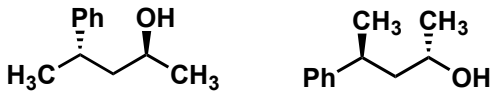


Workshop Problems

Workshop Problem 1: Stereochemistry

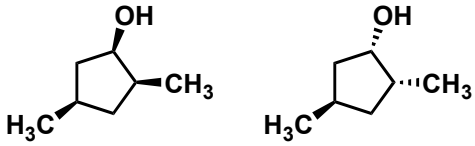
Indicate whether each structure below is chiral or achiral; then, indicate whether the pairs of structures represent identical molecules, structural/constitutional isomers, diasteromers, or enantiomers.

1-a.



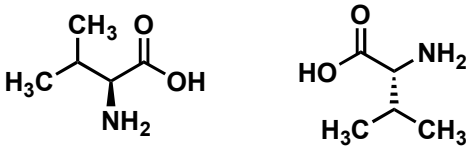
both chiral, identical molecules

1-b.



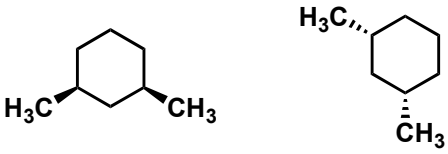
both chiral, diastereomers

1-c.



both chiral, enantiomers

1-d.

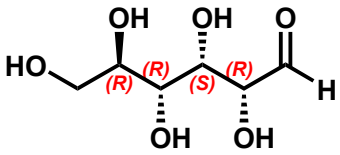


both achiral (meso), identical molecules

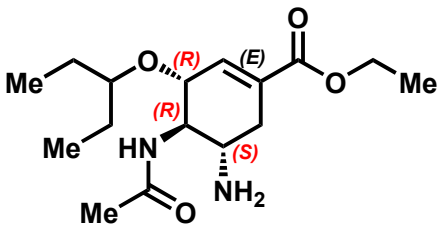
Workshop Problem 2: Assigning R/S and E/Z

For each of the small molecules shown below, use the CIP convention to assign all stereocenters as (*R*) or (*S*), and identify alkenes as (*E*) or (*Z*).

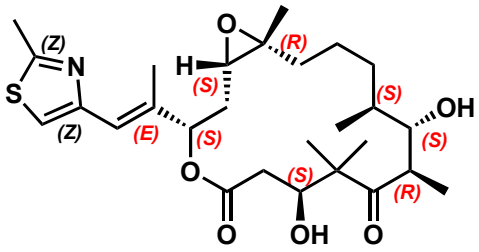
2-a. Glucose (linear form)



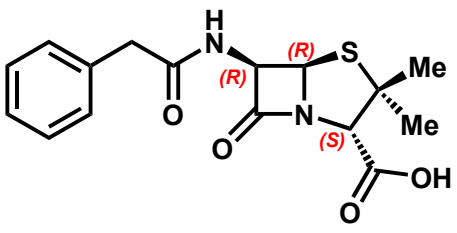
2-b. Tamiflu



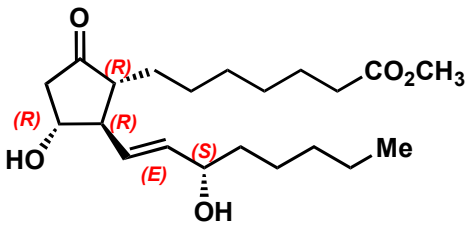
2-c. Epothilone



2-d. Penicillin V

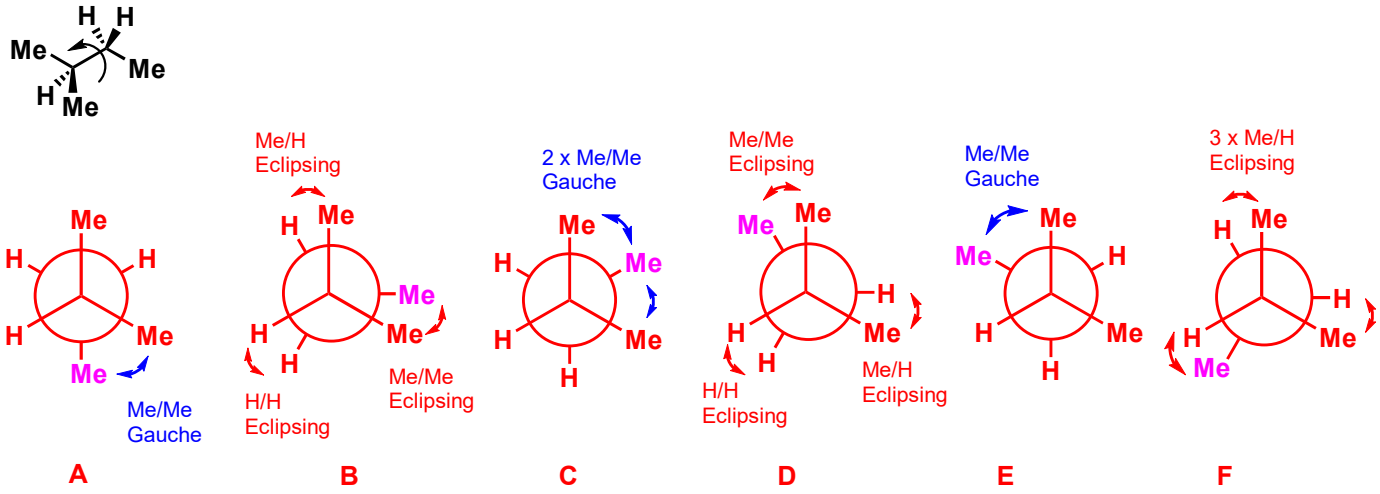


2-e. Prostaglandin E_1

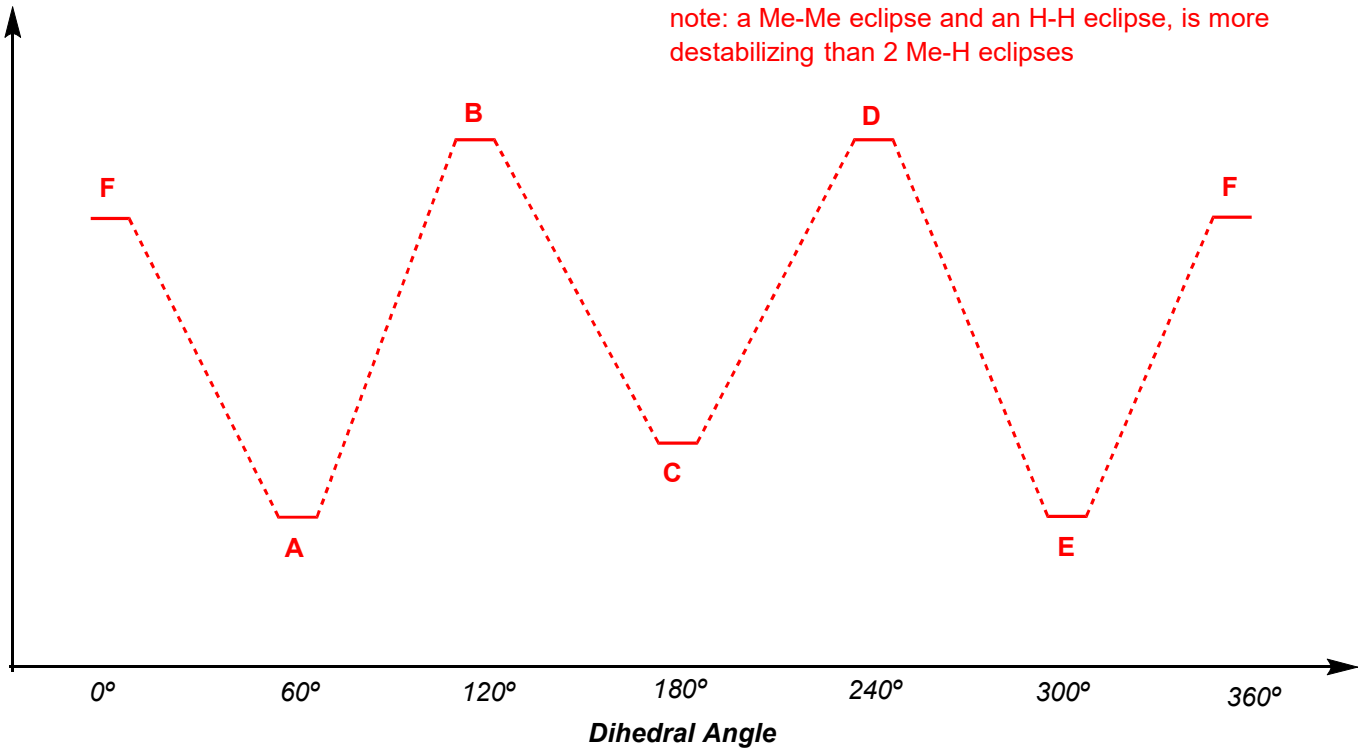


Workshop Problem 3: Conformational Analysis of Acyclic Systems

3-a. Provide a Newman projection corresponding to each energy minimum and maximum for rotation about the central bond of 2-methylbutane. For each conformer, identify all of the gauche and eclipsing interactions.



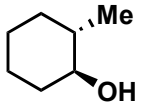
3-b. In the space below, construct an energy diagram that shows the relative conformational energies of 2-methylbutane upon 360-degree rotation about the central bond. All local energy minima and maxima should be connected with a smooth curve. For clarity, you may label the Newman projections in part **a** (A, B, C . . .) and use those labels on your diagram below.

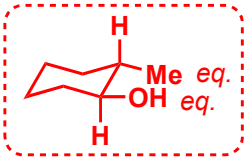


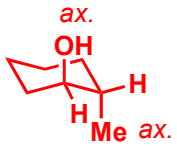
Workshop Problem 4: Conformational Analysis of Cyclic Systems

For each of the compounds below, draw all the energetically accessible chair conformations, and circle the most stable conformation(s). In each conformation, label the non-hydrogen substituents as axial or equatorial.

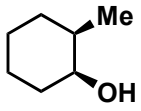
4-a.

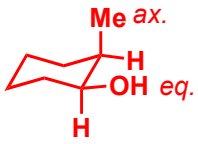


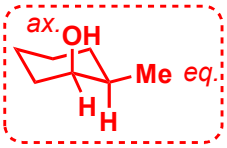




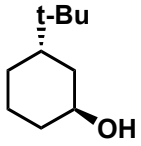
4-b.

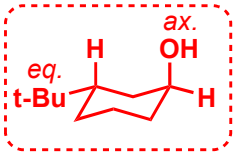




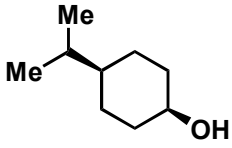


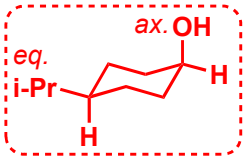
4-c.

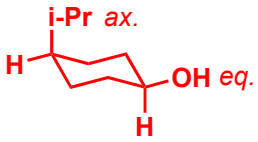




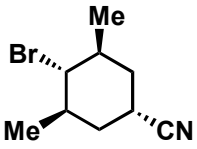
4-d.

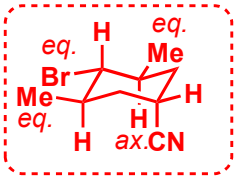


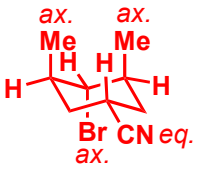




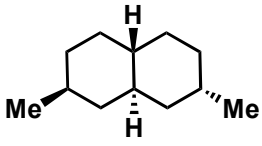
4-e

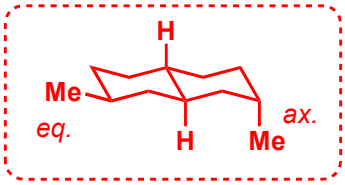






4-f





Practice **Problems**

Skillbuilder problem 1: Indicate whether each structure below is chiral or achiral; then, indicate whether the pairs of structures represent identical molecules, structural/constitutional isomers, diasteromers, or enantiomers.

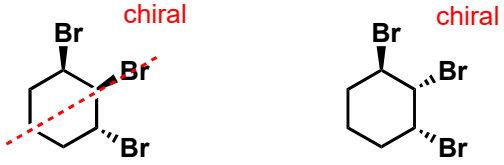
1-a

achiral chiral

constitutional isomers

1-e

chiral chiral



identical molecules (try rotating around the axis indicated)

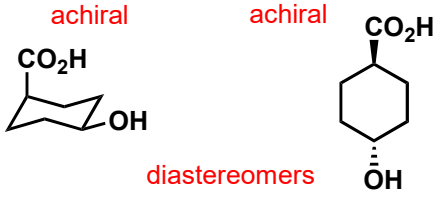
1-b

achiral achiral

diastereomers

1-f

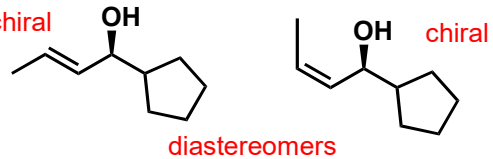
achiral achiral



diastereomers

1-c

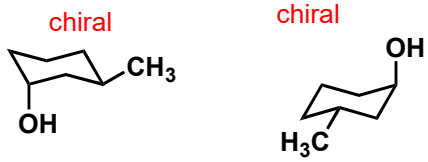
chiral chiral



diastereomers

1-g

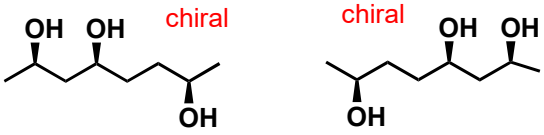
chiral chiral



identical molecules (draw as flat and rotate)

1-d

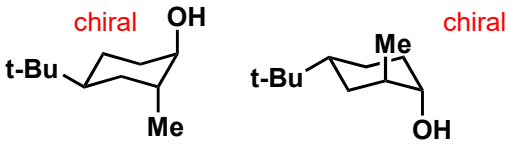
chiral chiral



enantiomers

1-h

chiral chiral

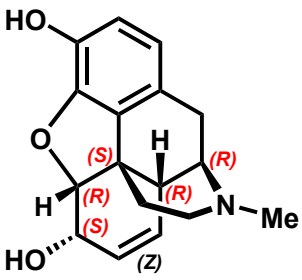


enantiomers

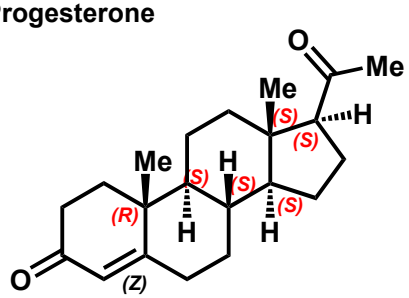
Skillbuilder Problem 2: Assigning R/S and E/Z

For each of the small molecules shown below, use the CIP convention to assign all stereocenters as (*R*) or (*S*), and identify alkenes as (*E*) or (*Z*).

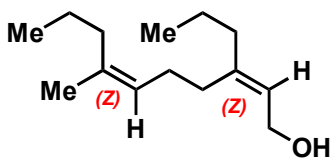
2-a. Morphine



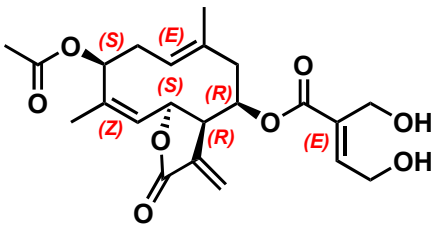
2-b. Progesterone



2-c. Codling moth compound

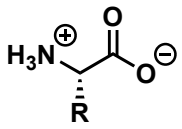


2-c. Eucannabinolide



Challenge Problem 1:

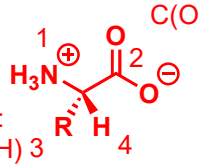
All of the α-amino acids encoded known as proteinogenic amino acids, have the general structure shown below, where R represents the sidechain group. With the exception of glycine (R = H), all of the α-amino acids have a stereocenter at the α-C, and so have the same "handedness". However, not all of the chiral α-amino acids have the same absolute configuration at this stereocenter, with cysteine being different from all of the others (which are the same). Explain this apparent inconsistency between structure and absolute configuration using the structures of several representative amino acid sidechains given below.



general structure

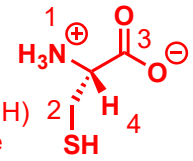
Cysteine, R = $-CH_2SH$
Valine, R = *i*-Pr
Serine, R = $-CH_2OH$
Aspartate, R = $-CH_2CO_2H$
Histidine, R =

C(O, O, O)



example:
C(O, H, H) serine

The priority order for all amino acids (except cysteine) is shown to left - this results in an absolute configuration of *S* (remember to put the lowest priority group to back!). The 4 other amino acids shown (and all other proteinogenic acids) have either C or O as the highest priority atom in the siechain in the next sphere out from the C.

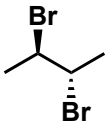


C(S, H, H) cysteine

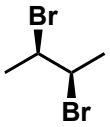
In cysteine the priorities of groups 2 and 3 are reversed because cysteine has a sulfur atom directly attached to the $-CH_2-$ group, which "wins" over O. This has the effect of reversing the absolute configuration label to *R*, despite the fact that all the amino acids appear to be of the "same hand", due to the same spatial sense in which the 4 groups are arranged around the stereocenter.

Challenge Problem 2:

Two of the stereoisomers of 2,3-dibromobutane are shown below. Draw the lowest and highest energy conformations of each molecule as Newman projections and as Sawhorse projections. Indicate clearly the presence of an internal mirror plane in any of these projections, and decide which of the two stereoisomers is the meso compound.



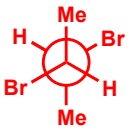
R, S stereoisomer

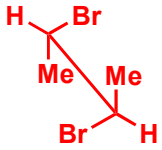


R, R stereoisomer

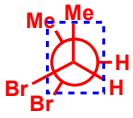
no conformation you can draw has an internal mirror plane. This compound is therefore chiral.

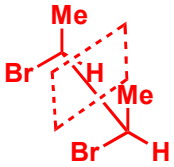
lowest





highest

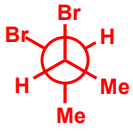


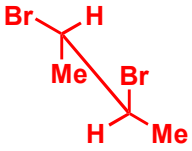


mirror plane here, so this is meso and achiral.

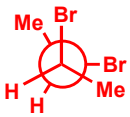
mirror between front and back carbons

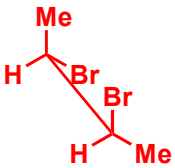
lowest



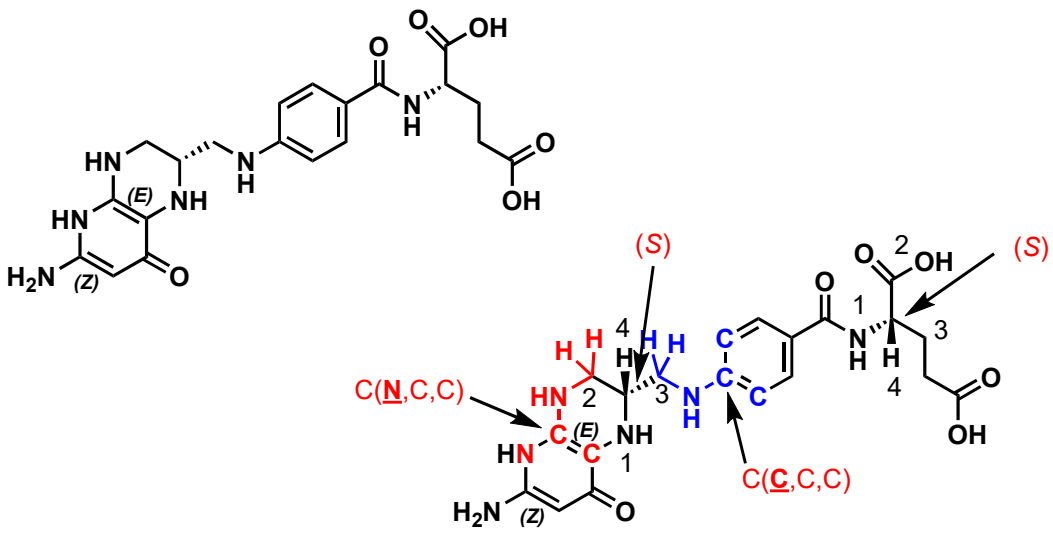


highest



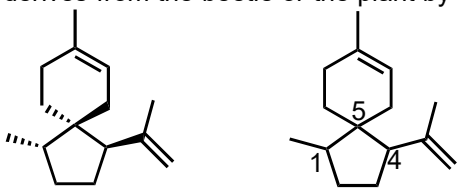


Challenge problem 3:
Assign the absolute configuration of the stereocenters in tetrahydrofolic acid, a cofactor involved in metabolism.



1st point of difference is in the 4th sphere of atoms away from stereocenter!

Challenge problem 4:
Acoradiene and its enantiomer are both naturally-occurring molecules, biosynthesized by completely different organisms. One enantiomer is an aggregation pheromone of the broad-horned flour beetle, whereas the other enantiomer is produced by the plant *Juniperis rigida*. The absolute configurations of all stereocenters of both enantiomers are given below, along with a numbering scheme for the compound. Decide whether the acoradiene structure drawn derives from the beetle or the plant by circling the appropriate option.



acoradiene

beetle 1*S*, 4*R*, 5*R* plant 1*R*, 4*S*, 5*S*